PYRROLIZIDINE ALKALOIDS. XVIII.*
CHIROPTICAL PROPERTIES OF SOME PYRROLIZIDINE ALKALOIDS

†J.Hrbek jr[a,**], L.Hruban[a,**], A.Klásek[a], N.K.Kochetkov[b], A.M.Likhosherstov[b], F.Šantavý[a] and G.Snatzke[c]

[a] *Institute of Chemistry, Faculty of Medicine, Palacký University, Olomouc,*
[b] *Zelinsky Institute of Organic Chemistry, Academy of Sciences of USSR, Moscow, USSR, and*
[c] *Institute of Organic Chemistry, University of Bonn, Bonn, GFR*

Received November 29th, 1971

The CD of some pyrrolizidine bases, their acyclic and cyclic esters as well as that of some necic acids has been measured by using various solvents. The tertiary amino group, the double bond and the ester group give rise to Cotton effects. In general, these are, however, not additive, which indicates differences in conformation of components in the free and the esterified state. CD is a very sensitive probe for the detection (in unpolar solvents) of the presence of the aminoketone tautomer of othonecine esters.

Pyrrolizidine alkaloids are mainly found in *Senecio* and *Crotalaria* species[3,4].*** They are mostly present as esters of pyrrolizidine bases with mono- or dicarboxylic acids though, occasionally, free amino alcohols have also been found in some of the plants. Since these two components contain chromophores which give rise to circular dichroism (CD), their Cotton effects are treated first.

Aminoalcohols with Pyrrolizidine Skeleton

The amine chromophore of platynecine[3,4] (*I*) gives rise to one or two bands in the wavelength range of 240–190 nm which are ascribed to $n - \sigma^*$ transitions because they disappear after acidification of the solution[5,6]. The skeleton of platynecine is symmetrical and optical activity is due only to different substitution at $C_{(1)}$ and $C_{(7)}$.† Therefore, only a small CD is expected. This is in agreement with the finding of $\Delta\varepsilon_{max} = +0{\cdot}5$ at 200 nm in ethanolic solution (Fig. 1*a*). The two epimeric alcohols heliotridine[3] (*II*) and retronecine[3,4] (*III*) give stronger Cotton effects with positive

* Part XVII: see Ref.[1]. This paper is also Part XLIV of the Bonn series on circular dichroism[2], and Part XVI of the Moscow series on pyrrolizidine alkaloids.

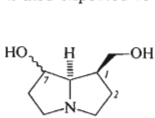
** 1968–1970 guests in Bonn.

*** Original literature cited only, if not covered by reviews[3,4].

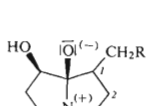
† In this paper, the atoms of the pyrrolizidine system have been numbered 1, 2 ..., those of the necic acids 1′, 2′, ... or 1″, 2″, ...

sign at about 214 nm (Fig. 1*a*). This increase in the CD as well as the bathochromic shift can be accounted for by the presence of a double bond which makes the environment of the N-atom less symmetrical. The UV-spectrum is, however, in these β,γ-unsaturated amines not influenced by such a π-system[7]. The difference in magnitude of the CD of *II* and *III* is probably not due to the direct effect of the OH-substituents ("third sphere effects"[8]) but to a conformational change in the saturated ring due to different sterical interactions between the OH— and the CH_2OH-groups (change of second sphere[8,9]). The three compounds mentioned above do not give a CD in aqueous hydrochloric acid contrary to the hydrochloride of *III* which in ethanolic solution shows a moderately strong positive CD at 193 nm. This band obviously results from an excitation of the double bond system which is also known to give a Cotton effect in chiral environment[10–13].

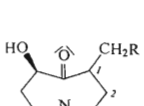
Compounds like othonecine (*IV*) do not exhibit spectral properties of a ketone. Therefore in solution, they are present exclusively or mainly as a zwitterion *IVa*. In accordance with this finding we could not detect any CD of dihydrodeoxy othonecine[14] (*V*) (in form of its hydrochloride, which is known to be present in the protonated form derived from *Va*), though the Cotton effect of the ketone group (formula *Vb*) is also expected to be very small.



I, 7 βOH
II, 7 αOH, $\Delta^{1,2}$
III, 7 βOH, $\Delta^{1,2}$



IVa, R = OH, $\Delta^{1,2}$
Va, R = H



IVb, R = OH, $\Delta^{1,2}$
Vb, R = H

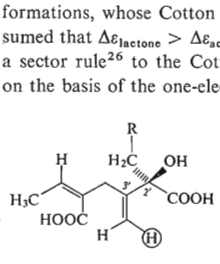
Necic Acids and Their Derivatives

Seneciphyllic acid[3] (*VI*) contains a conjugated and a homoconjugated COOH-chromophore. In principle, both of them may be optically active[15,16]. However, we could not detect with certainty an $n - \pi^*$ band of the first which should show up at about 240–250 nm. The Cotton effect found (Fig. 1*b*) at 217 nm (−2·3) will probably originate from the $n - \pi^*$ transition of the β,γ-unsaturated acid grouping which is much closer to the chiral center than the other COOH-group. Due to the steric hindrance caused by the hydrogen atom marked with a circle in formula *VI*, the CO-bond of the $C_{(1')}$ carboxyl will not be eclipsed to the 2′–3′ bond, which is otherwise the preferred conformation of acids in the crystal[17,18] and in solution[19]. The negative sign of this CD-band determines the relative geometry between the C=O and C=C system[15,16] but the thus derived arrangement is still in agreement

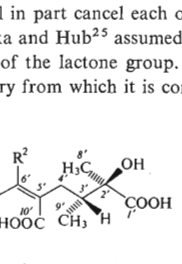
with several possible conformations. To a smaller extent, the CD at 217 nm may also be due to the $\pi - \pi^*$ absorption of the conjugated acid[20]. The CD spectrum of riddellic acid[3] (*VII*) is almost identical to that of *VI*. Since hydrogen bridges are of no great importance in ethanolic or acidic solution, the CD provides evidence for the same absolute configuration at $C_{(2')}$ for the acids *VI* and *VII*. This implies that seneciphyllic acid (*VI*) has the (2′*R*)-configuration and riddellic acid (*VII*) the (2′*S*)-configuration.

Senecic acid[3,4] (*VIII*), a dihydro derivative of *VI*, shows two CD-bands at 234 (positive) and at 210 nm (negative) (Fig. 1*b*). This behaviour is at first glance reminiscent of the recent findings made in the case of other α-hydroxy acids[21–24]. Since, however, the CD of the long wavelength band is larger than that at 210 nm, it is assumed that the 234 nm CD band is also attributable at least in part to the $n - \pi^*$ transition of the conjugated acid function though it is located at relatively short wavelengths. The band at 210 nm is composed of the K-band of this chromophore and of the $n - \pi^*$ band of the $C_{(1')}$ carboxylic group. In view of this band overlap, we can draw no conclusions about the preferred conformation of the hydroxy acid moiety of the molecule. On the other hand, the carbonyl oxygen of the carboxyl group $C_{(6')}$ (presumably present in a *transoid* conformation) will have to lie above the plane of the paper (formula *VIII*) due to steric interaction with the methyl group at $C_{(3')}$ and the chirality of the en-acid system will indeed lead to a positive CD[15,16]. Integerrinecic acid[3,4] (*IX*) is the corresponding *trans* (*E*) compound to *VIII*; it also has a positive CD band at 233 nm. The very small negative CD band at 257 nm may be ascribed to the above mentioned Cotton effect of α-hydroxy acids[21–24]. The sense of the torsion angle around the 5′–6′ bond should not be influenced pronouncedly by the change in the geometry at $C_{(7')}$ and the same sign for the 233 nm band in the CD spectra of *VIII* and *IX* is, therefore, expected.

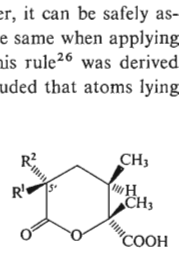
Dihydrosenecic lactone[25] (*X*) contains an acid and a lactone chromophore. Both can give rise to CD. Since, however, the carboxylic group can adopt several conformations, whose Cotton effects will in part cancel each other, it can be safely assumed that $\Delta\varepsilon_{lactone} > \Delta\varepsilon_{acid}$. Červinka and Hub[25] assumed the same when applying a sector rule[26] to the Cotton effect of the lactone group. This rule[26] was derived on the basis of the one-electron theory from which it is concluded that atoms lying



VI, R = H
VII, R = OH



VIII; $R^1 = CH_3$, $R^2 = H$
IX; $R^1 = H$, $R^2 = CH_3$



X; $R^1 = H$, $R^2 = C_2H_5$
XI; $R^1 + R^2 = \begin{matrix} H \\ H_3C \end{matrix}\!\!>\!C=$

in nodal spheres do not contribute to the CD. This implies that in the case of a butanolide or a pentanolide, the second sphere effects are zero. However, the more recent results obtained from the adamantanone series[27] as well as those from disubstituted indane derivatives[28] showed that the polarizability theory is a better approximation to correlation of the Cotton effect with stereochemistry. When taking into account bond polarizabilities, we must not neglect the second sphere effects because *e.g.* three bonds of the pentanolide ring are not lying in nodal spheres. A sector rule of that type described earlier[26] should thus be applicable only in the case of lactones (esters, acids) with a coplanar ring. When a chiral second sphere is present, the rule put forward by Legrand and Bucourt[29], and Wolf[30], respectively, is a more appropriate description. For *X*, the ring cannot adopt a boat conformation[30] because in that case at least one substituent would have to be in a flag-pole position. The negative sign of the CD (−3·41 at 218 nm), which according to the assumption discussed above comes mainly from the lactone chromophore, indicates that the torsion angle around the 5′−6′ bond is positive. This conformation is only possible if the ethyl group is quasi-equatorial and, therefore, in *cis*-position to the acid group $C_{(1')}$ (Fig. 2). On the basis of these findings, the definite configuration of *X* is (2′*R*, 3′*R*, 5′*R*). A small

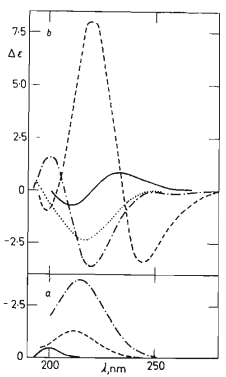


FIG. 1

a CD Curves of Platynecine (*I*) ———, Heliotridine (*II*) – – – – and Retronecine (*III*) –·–·–·– in Ethanol; *b* CD Curves of Senecifhyllic Acid (*VI*) ·····, Senecic Acid (*VIII*) ———, Senecic Lactone (*XI*) –·–·–·– and Clivoric Acid (*XIV*) – – – – – in Ethanol

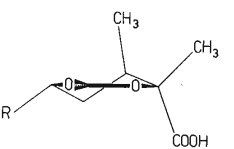


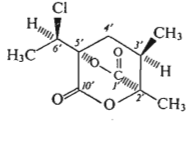
FIG. 2

Projection of Dihydrosenecic Lactone (*X*) Showing the Halfchair Conformation which Gives Rise to a Positive Torsion Angle Around the 5′—6′-Bond

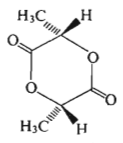
shoulder in the CD at about 260 nm may again correspond to the long wavelength band of hydroxy acids[21-24].

The conjugated lactone chromophore of senecic lactone[4] (*XI*) gives rise to a negative R-band CD (at 261 nm) and to a K-band CD of the same sign (at 220 nm) (Fig. 1*b*). The positive band at 201 nm can be ascribed to the $n - \pi^*$ transition of the acid chromophore. It is shifted to shorter wavelengths because of band overlap (relevant calculations[31,32]). From models, the enelactone system seems to be coplanar. Since, so far, we have no rule for such a *cisoid* enone type chromophore, we cannot predict a preferred conformation for the ring of *XI*.

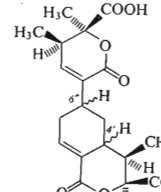
The absolute configuration of chlorojaconecic dilactone (*XII*) is known[33]. The two $n - \pi^*$ transitions are not supposed to give rise to exciton splitting because they are forbidden and their electric transition moment vector is thus very small. Each lactone chromophore is, at the same time, incorporated into two rings with opposite torsion angles around the respective (O=)C—C_α bonds (Fig. 3). The effects of the second spheres will, therefore, cancel each other to some extent. Since, however, the polarizabilities for the two C_α—C_β-bonds are different in the "monolactone ring" ($C_{(1')}$,···$C_{(5')}$) and the "dilactone ring" ($C_{(1')}$, $C_{(2')}$, O, $C_{(6')}$, $C_{(5')}$, O) of each chromophore, there is no exact compensation of second sphere effects, and one of the two second spheres must be preponderant for the CD. According to Fig. 1b, both chromophores must then give contributions to the CD which have identical signs. From the negative torsion angle in the "monolactone ring", a positive CD is predicted[29,30] and from the positive angle in the "dilactone ring" a negative one. The observed CD is positive, which indicates that for approximately equal torsion angles $\Delta\varepsilon$ of the pentanolide ring is bigger than that of its 3-oxa analogue. The CD of (*S*,*S*)-lactide (XIII), prepared from (*S*)-lactic acid in connection with work on the Cotton effects of lactones, was recently reported to be negative[34]. Though resembling in part the dilactone *XII*, this compound is not a good model for it because it is not rigid. On the basis of the results obtained from application of the corresponding rule[29,30], positive torsion angles around the (O=)C—C_α bonds of *XIII* are assumed. This



XII



XIII



XIV

conformation brings the methyl groups into equatorial positions, and is thus similar to that recently found to be prevailing in the corresponding 2,5-piperazinediones[35].

Clivoric acid[1,36,37] (*XIV*) is a dimer which can be rationalized to originate from a Diels-Alder addition of two double bond isomers of clivonecic acid[38] (*XV*). It shows a negative R-band CD for conjugated enelactone chromophores, a strongly positive CD band at 220 nm (K-band), and a smaller negative one at 199 nm (Fig. 1*b*). In view of the steric course of the Diels–Alder reaction, the two hydrogen atoms at the angular positions 4′ and 6″ must be *trans* to each other. This implies either an axial conformation for the hexenolide substituent, which could lead to a vicinal effect between the two chromophores, or a stronger deviation from coplanarity for the *cisoid* enelactone chromophore. In both cases relatively strong Cotton effects such as indeed found by us can be expected. However, in view of the presence of two overlapping pairs of CD bands, no conclusions can be drawn from the CD curve about the absolute stereochemistry at the newly introduced chiral centers.

Monocrotalic acid[4] (*XVI*) also has two chromophores, *viz.* an acid group and a lactone in a five-membered ring whose absolute configuration at $C_{(2')}$, $C_{(3')}$, and $C_{(4')}$ is known[25,39,40]. When assuming as in the preceding cases that the CD of *XVI* comes mainly from the lactone and not from the acid chromophore, a positive torsion angle around the 4′–5′ bond follows from the negative CD (at 218 nm). Such a conformation is indeed found from molecular models when the methyl group at $C_{(4')}$ is positioned (quasi)equatorially. $C_{(4')}$ is the only C-atom of the lactone ring which is monosubstituted. The Cotton effect of the simple model compound *XVII* and its methyl ester of unequivocally known absolute (*S*)-configuration was found to be positive[41]. Accordingly, the torsion angle around the 4′–5′ bond must be negative. This is again in agreement with the conformational analysis since a (quasi)-equatorial position of the only substituent (the COOR group) actually causes such a sign of the respective torsion angle. Erucifolinecic acid[42,43] (*XVIII*) is assumed to be a tetrahydrofurane. It is formed by addition of a hydroxyl group at $C_{(3')}$ (after opening of the epoxy-grouping) to the double bond of the conjugated acid grouping. It exhibits a small negative CD whose maximum could not be reached completely. This is in agreement with the formulation of *XVIII* as a saturated (di)acid.

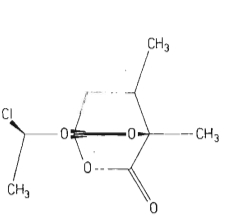
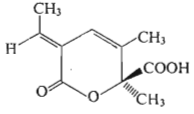
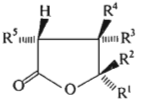


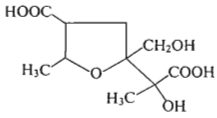
FIG. 3

Projection of Chlorojaconecic Dilactone (*XII*) onto a Plane Orthogonal to the Plane of the 6′-Lactone Group

Since the CD of the ester alkaloids was also determined for acidic solution, we have measured the CD of these acids and lactones not only in ethanol but also in 1M-HCl. In general, there is no fundamental difference between the values for the two solvents, except for those of *XI* and *XVIII* where a CD maximum at short wavelengths could be detected.





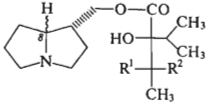


XV *XVI*; $R^1 = COOH$, $R^2 = R^3 = R^5 = CH_3$, $R^4 = OH$ *XVIII*

XVII; $R^1 = R^3 = R^4 = R^5 = H$, $R^2 = COOH$

Ester Alkaloids Containing Saturated Monocarboxylic Acids

Lindelofine[3] (*XIX*) shows a positive CD band at 204 nm in ethanol solution (Fig. 4*a*), whereas in hydrochloric acid only a very weak Cotton effect at 215 nm is detectable. The latter effect may also be present in the spectrum of the ethanolic solution but it is so small that it cannot even produce a shoulder in the CD curve. The disappearance of the 204 nm CD band in acidic solution indicates that the positive Cotton effect of about +1 comes from the $n - \sigma^*$ transition of the (esterified) basic moiety lindelofidine. The positive sign of the very weak ester CD band (at 215 nm) is the same as that for ethyl L-lactate[21-24]. However, it cannot be directly compared with the latter, because it contains a tertiary instead of a secondary hydroxyl group. On the contrary, trachelanthamine[3] (*XX*) shows only a very weak positive CD at 215 nm in ethanolic solution. In hydrochloric acid, the CD curve is similar to that in ethanol and, as expected, identical with that of *XIX*. The contribution to the CD of (esterified) trachelanthamidine, the basic moiety of *XX*, is obviously very small, which is reasonable for a pyrrolizidine system with *cis*-configuration of the side chain and the H at $C_{(8)}$. With such a configuration, the two oppositely twisted conformations of the pyrrolizidine system have similar energy contents, whereas in the diastereomer *XIX* with *trans*-configuration, in view of the molecular models one form appears to be much more preferred than the other.



XIX; 8 βH, $R^1 = H$, $R^2 = OH$
XX; 8 αH, $R^1 = H$, $R^2 = OH$
XXI; 8 βH, $R^1 = OH$, $R^2 = H$
XXII; 8 αH, $R^1 = OH$, $R^2 = H$

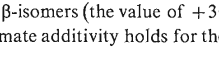
Cynaustraline[3] (*XXI*) was available to us only in form of a hydrochloride, which did not give a detectable CD in ethanolic solution. Its 8α-isomer viridiflorine[3] (*XXII*) showed small positive CD bands in both solvents at 214 nm, which is in agreement with the result obtained for trachelanthamine (*XX*). Only the ester chromophore of *XX* and *XXII* has a g'-value[44] (defined as $g' = \Delta\varepsilon/\varepsilon$) big enough to give rise to an observable CD band whose sign is the same as that for *XIX* with identical stereochemistry at the C-atom of the acid. Supinine[3] (*XXIII*) (Fig. 4*a*) and its 3'-O-methyl ester heleurine[3] (*XXIV*) give a positive CD at about 216 nm in ethanolic solution (+2·24 and +1·28, resp.). It becomes smaller in hydrochloric acid (+0·42 for *XXII*, indetectable for *XXIV*). Therefore, the corresponding base supinidine must give rise to a positive CD band, which is in agreement with the fact that the two unsaturated bases heliotridine (*II*) and retronecine (*III*) also give a positive CD. The acid moiety of *XXIII* is the same as that of the alkaloids *XIX* and *XX* (trachelanthic acid). Consequently, in these three cases, the same sign for the CD of the ester chromophore is observed.

Echinatine[3] (*XXV*) gives a detectable CD only in ethanolic solution (+1·93), which is similar to that of the corresponding free base heliotridine (*II*). A similar CD value was found for heliotrine[3,4] (*XXVI*) which is another ester with the same base. It exhibits a small positive CD band in acidic solution, which is consistent with the (*S*)-chirality at the $C_{(2')}$-atom of the acid moiety. The fact that we could not always detect the presence of an ester CD band in acidic medium has technical reasons. The absorption of the unsaturated pyrrolizidine derivatives is already relatively high due to the additional double bond so that the necessary concentration for the detection of this small Cotton effect cannot always be used. Europine[3] (*XXVII*), whose base is also heliotridine (*II*), shows the expected positive CD in ethanolic solution. In hydrochloric acid the CD is too small to be detected unequivocally. For indicine[3] (*XXVIII*), we could again find a CD only in neutral solution. It is positive and bigger than that of *XXV*, *XXVI*, or *XXVII*, which is in agreement with the fact that the magnitude of the Cotton effect is also increased by isomerization at $C_{(7)}$ in the free base (from 7α- to 7β-OH).

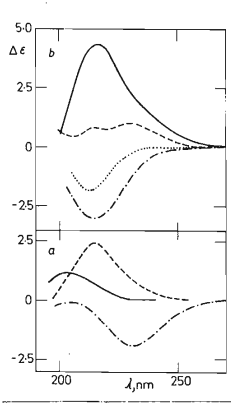
Ester Alkaloids with Unsaturated Monocarboxylic Acids

Echiumine[3,4] (*XXIX*) is 7β-angeloylsupinine; as in the case of other 7β-oxygenated bases, a somewhat higher CD is expected for this alkaloid. The values of +6·71 in ethanolic solution and +2·87 in hydrochloric acid are, however, too big to come from the supinine part of the molecule. Obviously, the K-band of the angeloyl residue is also optically active with a contribution of about +4 to +5 to the 223 nm CD band. If similar conformations for the base and its hydrochloride are assumed, the contribution of the doubly esterified retronecine (*III*) to the CD at about 220 nm can be calculated to be +3·9. In the CD spectrum of *XXIX*, the R-band of the ange-

loyl residue does not give a detectable Cotton effect, such is the case, however, with rivularine ($O_{(7)}$-angeloyl heliotridine)[3] (*XXX*) and lasiocarpine[3] (*XXXI*). The latter two give small negative Cotton effects around 250 nm. In these 7α-oxygenated compounds, the contribution of the K-band of the angeloyl residue to the CD at about 211 nm is moderately positive, *viz.* +1·7 ($\Delta\varepsilon_{XXX} - \Delta\varepsilon_{II}$), and +1·2, ($\Delta\varepsilon_{XXXI} - \Delta\varepsilon_{XXVII}$), respectively – both values obtained by curve subtraction. The contribution of the basic component of *XXX* and *XXXI* to the same band is +3·4 and +2·9, respectively. This is in good agreement with the fact that 7α-oxygenated compounds give a somewhat smaller CD than their 7β-isomers (the value of +3·9 for *XXIX*). Consequently, in these alkaloids, an approximate additivity holds for the contributions to the Cotton effect.



XXIII; $R^1 = R^2 = R^3 = H$, $R^4 = R^5 = OH$, $R^6 = (CH_3)_2CH$
XXIV; $R^1 = R^2 = R^3 = H$, $R^4 = OCH_3$, $R^5 = OH$, $R^6 = (CH_3)_2CH$
XXV; $R^1 = R^3 = R^5 = OH$, $R^2 = R^4 = H$, $R^6 = (CH_3)_2CH$
XXVI; $R^1 = R^5 = OH$, $R^2 = R^3 = H$, $R^4 = OCH_3$, $R^6 = (CH_3)_2CH$
XXVII; $R^1 = R^5 = OH$, $R^2 = R^4 = H$, $R^3 = OCH_3$, $R^6 = (CH_3)_2(OH)C$
XXVIII; $R^1 = R^4 = H$, $R^2 = R^3 = R^6 = OH$, $R^5 = (CH_3)_2CH$
XXIX; $R^1 = R^3 = H$, $R^2 = $ Angeloyl, $R^4 = R^5 = OH$, $R^6 = (CH_3)_2CH$
XXXI; $R^1 = $ Angeloyl, $R^2 = R^4 = H$, $R^3 = OCH_3$, $R^5 = OH$, $R^6 = (CH_3)_2(OH)C$



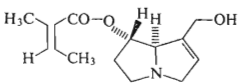
In sarracine[3,4] (*XXXII*), both esterifying acids are unsaturated, whereas the base platynecine (*I*) is saturated. Therefore, a direct comparison of its CD (negative at 230 nm in ethanol (Fig. 4*a*), in hydrochloric acid and additional positive band at 213 nm) with that of other angeloyl derivatives cannot be carried out.

FIG. 4

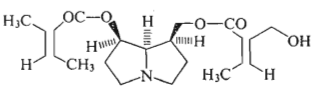
a CD of Lindelofine (*XIX*) ———, Supinine (*XXIII*) – – – – – and Sarracine (*XXXII*) –·–·–·– in Ethanol; *b* CD of Monocrotaline (*XXXIII*) in Ethanol ———, in 1M-HCl –·–·–·– and of Jacobine (*XXXV*) in Ethanol – – – – –, in 1M-HCl ·····

Cyclic Ester Alkaloids with Dicarboxylic Acids

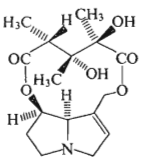
Monocrotaline[3,4] (*XXXIII*) shows a strongly positive CD in ethanolic solution (Fig. 4*b*) which is nearly identical with that of its basic moiety retronecine (*III*). In acidic solution, the CD of *XXXIII* is negative (Fig. 4*b*) and similar to that of monocrotalic acid (*XVI*). Since the hydrochloride of retronecine (*III*) does not give a CD at 215 nm, the Cotton effect at this wavelength in acidic solution must mainly come from the ester chromophores. It is, however, just accidental that the signs and even magnitudes of the CD bands in the spectra of *XXXIII* and *XVI* (acidic solution) are similar because both ester chromophores must contribute to the CD in *XXXIII*,



XXX



XXXII



XXXIII

whereas the Cotton effect of *XVI* is mainly coming from only one lactone chromophore. In neutral solution, the CD band at 216 nm is composed of Cotton effects obtained from the basic moiety retronecine (*III*) and the two ester groups. The contribution of the latter two must, however, not be necessarily the same in neutral medium and in hydrochloric acid. The formal contribution of +7·4 of the pyrrolizidine base to the CD is thus certainly due in part to a conformational change in the 11-membered diester group by going from the neutral form to the salt.

Jacoline[3,4] (*XXXIV*) contains – like nearly all of the alkaloids discussed below – a 12-membered diester ring. In neutral solution, its CD is again identical with that of retronecine (*III*), in hydrochloric acid it drops to about half of this value. The contribution of the base to the CD is thus about +2·3, which is in quite good agreement with the value obtained for the monoester indicine (*XXVIII*). This is, however, again fortuitous. Jacobine[3,4] (*XXXV*), which contains a spiro epoxide ring, exhibits a much smaller CD at 216 nm than retronecine (*III*) but the contribution of the base to the CD is again of the same magnitude as for *XXXIV*, *viz.* +2·6 (Fig. *4b*). From this fact, similar conformations of the diester ring in *XXXIV* and *XXXV* can be deduced because all chromophoric groups are similarly arranged. Surprisingly there

appeared another band at 230 nm which can be explained only by the assumption that in neutral solution the epoxide ring is disposed with respect to the $C_{(6')}$ ester grouping in such a manner that its oxygen atom is (quasi)axial to it. An α-axial OH-group, even though in the same position, has a much smaller influence upon the CD of a carbonyl compound than an epoxide ring. In hydrochloric acid, this band is not present which indicates a change in conformation, at least in the area around $C_{(5')}$, caused by acidification (Fig. 4*b*). In acidic solution, the CD spectrum of onetine[3] (*XXXVI*) is identical with that of jacoline (*XXXIV*) which evidences that in each of these alkaloids the diester ring containing jacolic acid adopts the same conformation in both salts. In neutral solution, onetine shows a very broad CD band with a shoulder at approximately 260 nm which indicates that to some extent the 8-keto form (analogue to *IVb*) is present in equilibrium with the zwitterion. The same is found for othosenine[3] (*XXXVII*) (Fig. 5*a*); in methylcyclohexane solution, this band is clearly discernible at 285 nm. It is even stronger than that at shorter wavelength. Even here some keto form must be present in solution though in the UV-spectrum in ethanol no distinct band could be discerned[20] and in methylcyclohexane the exhibited shoulder was only weak. Thus, also in this case, the CD is a more sensitive probe for detecting such tautomers in small concentration in solution than UV-spectroscopy. In acidic solution, the CD curve is again very similar to that of its analogue jacobine (*XXXV*) which contains retronecine (*III*) instead of othonecine (*IV*) as its base.

Platynecine (*I*), the basic moiety of neoplatyphylline[3] (*XXXVIII*), does not contribute appreciably to the CD of the alkaloid: the negative CD band at about 239 nm in neutral ($\Delta\varepsilon = -2{\cdot}04$) or acidic solution ($\Delta\varepsilon = -1{\cdot}31$) appears to arise from a transition of the conjugated ester grouping (probably its R-band, *cf.* the discussion for

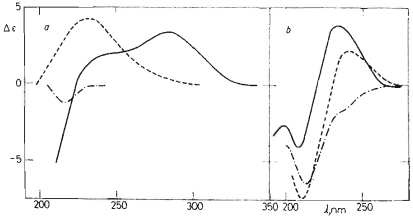
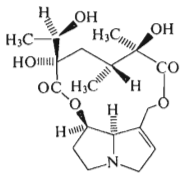


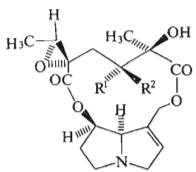
FIG. 5

a CD of Othosenine (*XXXVII*) in Methylcyclohexane ———, in Ethanol – – – – – and in 1M-HCl –·–·–·–; *b* CD of Platyphylline (*XXXIX*) –·–·–·–, Integerrimine (*XLI*) ——— and Senecionine (*XLIII*) – – – – – in Ethanol

VIII and *IX*). Due to incorporation into a ring, the acid is forced to adopt another conformation than in the free state, which leads to inversion (and augmentation) of the CD band compared to the corresponding band of *IX*. The second band appearing at about 210 nm in hydrochloric acid solution must also be an ester band ($n - \pi^*$ transition of the 1′-COO- and/or $\pi - \pi^*$ transition of the 6′-COO-chromophore). Platyphylline[3] (*XXXIX*), differing from *XXXVIII* only in the geometry of the double bond, gives a strongly negative Cotton effect at about 214 nm both in neutral and in acidic solutions (Fig. 5*b*). The long wavelengths band is also discernible though only as a (negative) shoulder. The *cis*-configuration of the methyl $C_{(8')}$ to the ester $C_{(6')}$ in *XXXIX* results in an increase in the K-band CD probably by fixation of a conformation with greater deviation from coplanarity of the C=C—C=O system. Rosmarinine[3] (*XL*), differing from platyphylline (*XXXIX*) only by an additional (2*S*)-hydroxy group, is supposed to give a similar Cotton effect to that of *XXXIX* because in view of molecular models this OH group does not seem to introduce severe steric interactions. The CD of *XL* in neutral as well as in acidic medium shows the same characteristic features as that of *XXXIX*.



XXXIV

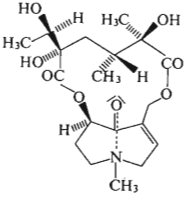


XXXV $R^1 = CH_3$, $R^2 = H$

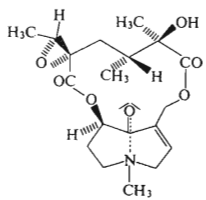
XLVIII $R^1 + R^2 = CH_2$

The two pairs of alkaloids, integerrimine[3,4] (*XLI*) and usaramine[3,4] (*XLII*) on the one hand, and senecionine[3,4] (*XLIII*) (Fig. 5*b*) and retrorsine[3] (*XLIV*) on the other differ only by the stereochemistry at the double bond. Within each group, the second compound always is the 2′-hydroxymethyl analogue to the first. The character of the CD-curve is not greatly changed by this substitution as expected for polar solvents where hydrogen bridging is unimportant. The CD band in the range 230 to 240 nm is always positive and at shorter wavelengths it is negative. Consequently, the positive contribution of the common base retronecine (*III*) to the Cotton effect is not even formally detectable in the CD curves of these alkaloids. Obviously, it is very small because there is no great change in going from free bases to salts. In accordance with the findings made for the pair *XXXVIII*/*XXXIX*, the 215 nm CD band is stronger negative by several $\Delta\varepsilon$-units in the case of the *cis*-configuration (*XLIII*, *XLIV*) of the $C_{(6')}$ ester grouping and the methyl $C_{(8')}$ than in the case of the

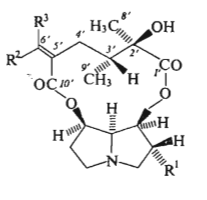
corresponding *trans*-compounds *XLI* and *XLII*. A comparison of these alkaloids can also be carried out in another way. On introduction of the 1,2 double bond into the base (*XXXVIII* → *XLI*, *XXXIX* → *XLIII*), the CD band at 240 nm reverses its sign and changes from $\Delta\varepsilon \approx -2$ towards $+2$ to $+4$. The unsaturated pyrrolizidines heliotridine (*II*) and retronecine (*III*) do not exhibit Cotton effects in this wavelength range. Consequently, this change in the CD reflects a reversal of the chirality of the C=C—C=O system whose $n - \pi^*$ transition is obviously responsible for this Cotton effect.



XXXVI



XXXVII

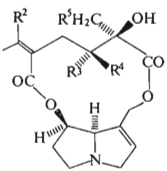


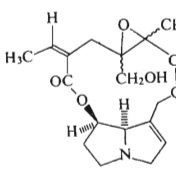
XXXVIII; $R^1 = R^2 = H$, $R^3 = CH_3$
XXXIX; $R^1 = R^3 = H$, $R^2 = CH_3$
XL; $R^1 = OH$, $R^2 = CH_3$, $R^3 = H$

The conformation of senecionine (*XLIII*) has been discussed by Culvenor[3] who assumes a *trans*-planar orientation of the C=C—C=O moiety. Though such an arrangement must also give rise to an $n - \pi^*$ Cotton effect in chiral environment, the inversion of the sign of the 240 nm band in the CD spectrum suggests a non-coplanarity of this system, which energetically will not be very much disfavoured, provided the deviation from the common plane is relatively small. In platynecine derivatives, the torsion angle between the C=O and C=C bonds should be positive because of the negative sign of the corresponding band, and a negative torsion angle follows from the positive sign for the cyclic retronecine diester[15,16]. An interaction between the two ester groupings (vicinal effect) through space, which could also influence the CD bands, cannot be completely excluded. The CD of senecionine (*XLIII*) in methylcyclohexane solution is very similar to that for ethanolic solution. Naturally, no tautomerism is possible for this alkaloid. The alkaloid erucifoline[42,43] (*XLV*) also contains retronecine (*III*) as basic component, the acid moiety is represented by a 2',3'-epoxy derivative of 3',9'-dihydroxysenecic acid (stereochemistry at the chiral centers still unknown). Therefore, the CD for ethanolic as well as acidic solution closely resembles that of senecionine (*XLIII*), which provides further proof for the stereochemistry around the double bond.

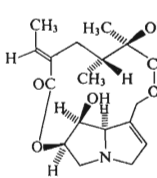
For madurensine[45] (*XLVI*), very recently evidence could be provided that the ester ring is not attached to the oxygen at $C_{(7)}$ but to that at $C_{(6)}$. The conformation of the diester ring system must be changed drastically. Indeed, its CD (ethanolic solution) is of enantiomorphic type to that of the aforementioned five alkaloids *XLI* to *XLV*. This clearly shows the importance of conformation for the correlation between CD and structure. Acidification causes a very strong change in the CD of *XLVI*, indicating again the different arrangement of this ring system.

Senkirkine (renardine[3], *XLVII*), though having a Z-configuration of the side chain double bond, gives rise to a CD which shows greater similarity to that of a 5',7'-*E* compound. In *XLVII*, this is obviously also due to the presence of some keto tautomer (analogue to *IVb*) which can be inferred from the much greater halfband width of the positive CD band at about 245 nm. Indeed, in methylcyclohexane solution, a CD band appears at 288 nm which is even more intense than that at 247 nm (similar changes in the CD spectra of *XXXVI* and *XXXVII*). It cannot be clearly discerned in the UV-spectrum. In acidic solution, these bands disappear completely indicating only the presence of a zwitterion. Furthermore, the negative CD band gains in rotational strength, which makes the CD curve more similar to that of the corresponding Z-compounds *XLIII* through *XLV*.





XLV



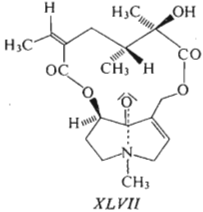
XLVI

XLI; $R^1 = R^4 = R^5 = H$, $R^2 = R^3 = CH_3$
XLII; $R^1 = R^4 = H$, $R^2 = R^3 = CH_3$, $R^5 = OH$
XLIII; $R^1 = R^3 = CH_3$, $R^2 = R^4 = R^5 = H$
XLIV; $R^1 = R^3 = CH_3$, $R^2 = R^4 = H$, $R^5 = OH$
XLIX; $R^1 = CH_3$, $R^2 = R^5 = H$, $R^3 + R^4 = CH_2$
L; $R^1 = CH_3$, $R^2 = H$, $R^3 + R^4 = CH_2$, $R^5 = OH$

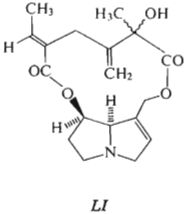
The CD of jacozine[3] (*XLVIII*) may be best compared with that of its dehydro analogue jacobine (*XXXV*) which gives only a small Cotton effect. The CD at 217 nm of *XLVIII* is, however, strongly negative. This might indicate that the double bond in the β,γ-position to the carboxyl group $C_{(1')}$ is arranged in such a manner that an enhancement of the Cotton effect is possible[15,16], *i.e.* in a negative octant. If the conformation of the diester ring is similar to that of jacobine bromohydrine (the pair *XXXIV*/*XXXV*), which is known from X-ray studies[46], then the double bond terminating at $C_{(3')}$ is in the right position for such an interaction. In acidic solution, the

CD of *XLVIII* is the same as that in neutral medium. Consequently, protonation of the nitrogen atom does not change the conformation of this molecule.

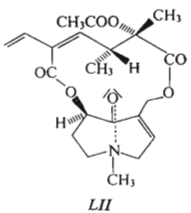
Seneciphylline[3,4] (*XLIX*) shows a positive $n \rightarrow \pi^*$ CD band of the conjugated ester grouping at 244 nm and a strongly negative band at 214 nm (−9·3). Both of them are somewhat more intense than those in the CD spectrum of senecionine (*XLIII*) which has a methyl group instead of a methylene grouping at $C_{(3')}$. The presence of the additional π-system has only a minor effect upon the CD of *XLIX*. Obviously, in *XLIX* the methylene group is not so favourably arranged as to give rise to a CD enhancement due to homoconjugation as it is the case in *XLVIII*. The CD of *XLIX* in methylcyclohexane is, as expected, the same as in ethanolic solution. A comparison carried out between the CD of the two analogues riddelline[3] (*L*) and retrorsine[3] (*XLIX*) shows that in this case the $n \rightarrow \pi^*$ CD band of the conjugated ester grouping is smaller for the 3'-methylene compound L than for the 3'-methyl compound *XLIV*. On the other hand, the CD band at 214 nm of *L* is somewhat stronger than that of *XLIV*. Consequently, the newly introduced double bond has also in this case only a minor influence upon the contribution of the ester grouping $C_{(1')}$ to the CD, as in the case with the very similarly constituted alkaloid seneciphylline (*XLIX*).



XLVII



LI



LII

In the CD spectrum of spartioidine[3] (*LI*), the 242 nm band is considerably smaller than that of its analogue *XLI* with a 3'-methyl group; the difference for the 208 nm band is smaller. Therefore, in this compound, the "homoconjugation" does not give rise to a strong enhancement of the Cotton effect of the carboxyl $C_{(1')}$.

Clivorine[1] (*LII*) is a macrocyclic diester of othonecine (*IV*) with a dicarboxylic diene acid. The CD spectrum of *LII* in ethanol solution is characteristic of the presence of a base of othonecine type, as it also gives the positive Cotton effect at about 260–280 nm, detectable as a tail in the 244 nm band. In methylcyclohexane solution, this band is more pronounced and has its maximum at 285. In acidic solution, this band disappears completely, thus indicating again the presence of some keto tautomer (like *IVb*) in neutral medium. Signs and magnitudes of the two CD bands at 244 and 219 nm (ethanolic solution) are similar to those of senecic acid esters (*cf. XLIII*),

in acidic solution there is, however, a great difference, since the positive CD band increases appreciably, and the negative one nearly disappears. Whether the diene "partial chromophore" is optically active in this compound or not cannot be derived from these spectra.

EXPERIMENTAL

The CD was recorded with a Roussel-Jouan dichrograph (Model 185) at 20°C in cells of 0·01 to 2·00 cm thickness, and a concentration of about 1 mg/g. All the values are given as $\lambda_{max}(\Delta\varepsilon)$, the inflexions are indicated by i. Abbreviations for solvents: E ethanol; M methylcyclohexane; HCl 1M-HCl.

Platynecine (I): E 200 (+0·5); HCl no CD detectable. *Heliotridine* (II): E 212 (+1·30). *Heliotridine*.HCl: E 199 (+0·6). *Retronecine* (III): E 215 (+3·7); HCl no CD detectable. *Retronecine*. HCl: E 193 (+4·7); HCl 218 (−0·05), positive at shorter wavelengths. *Dihydrodeoxy othonecine*. HCl (V): E, HCl no CD detectable.

Seneciphyllic acid (VI): E 217 (−2·3); HCl 216 (−2·1). *Riddellic acid* (VII): E 219 (−2·29); positive at shorter wavelengths; HCl 218 (−1·6). *Senecic acid* (VIII): E 234 (+0·96), 210 (−0·7); HCl 235 (+1·21), 210 (−1·2). *Integerrinecic acid* (IX): E 257 (−0·04), 233 (+0·27); HCl 228 (+0·5). *Dihydrosenecic lactone* (X): E 260i (−0·11), 218 (−3·41); HCl 218 (−2·37). *Senecic lactone* (XI): E 261 (−0·20), 220 (−3·62), 201 (+1·6); HCl 218 (−2·6). *Chlorojaconecic dilactone* (XII): E 236 (+1·31), 210 (−0·05); HCl 230 (+0·88). *Clivoric acid* (XIV): E 245 (−3·41), 220 (+7·98), 199 (−1); HCl 249 (−4·88), 220 (+5·28), 205 (−2). *Monocrotalic acid* (XVI): E 218 (−3·47), positive at shorter wavelengths; HCl 215 (−4·54). *Erucifolinecic acid* (XVIII): E negative (maximum not reached); HCl 216 (−1·5).

Lindelofine (XIX): E 204 (+1·17); HCl 215 (+0·10). *Trachelanthamine* (XX): E 217 (+0·08); HCl 216 (+0·11). *Cynaustraline*.HCl (XXI): E, HCl no CD detectable. *Viridiflorine* (XXII): E 214 (+0·22), HCl 214 (+0·44). *Supinine* (XXIII): E 215 (+2·24); HCl 215 (+0·42). *Heleurine* (XXIV): E 218 (+1·28); HCl no CD detectable. *Echinatine* (XXV): E 218 (+1·93); HCl no CD detectable. *Heliotrine* (XXVI): E 216 (+2·39), 201 (+2·3); HCl 215 (+0·27), positive at shorter wavelengths. *Europine* (XXVII): E 221 (+0·50); HCl no CD detectable. *Indicine* (XXVIII): E 213i (+2·68), 200 (+2·9); HCl positive (maximum not reached). *Echiumine* (XXIX): E 223 (+6·71), HCl 220 (+2·87). *Rivularine* (XXX): E 245 (−0·31), 208 (+2·55); HCl 245 (−0·28), 210 (−0·5). *Lasiocarpine* (XXXI): E 253 (−0·21), 214 (+1·5); HCl 214 (−1·4). *Sarracine* (XXXII): E 230 (−1·97); HCl 236 (−3·31), 213 (+3·12).

Monocrotaline (XXXIII): E 216 (+4·38); HCl 214 (−3·0). *Jacoline* (XXXIV): E 216 (+3·91); HCl 215 (+1·62), stronger positive at shorter wavelengths. *Jacobine* (XXXV): E 230 (+1·09), 216 (+0·80); stronger positive at shorter wavelengths; HCl 212 (−1·78). *Onetine* (XXXVI): E 260i (+1·53), 217 (+5·59); HCl 214 (+1·34), stronger positive at shorter wavelengths. *Othosenine* (XXXVII): E 270i (+0·87), 231 (+4·38); HCl 216 (−1·20); M 285 (+3·57), 245i (+2·07), negative at shorter wavelengths. *Neoplatyphylline* (XXXVIII): E 238 (−2·04); HCl 240 (−1·31), 210 (−1·9). *Platyphylline* (XXXIX): E 235i (−1·74), 214 (−6·4); HCl 241i (−0·71), 213 (−3·2). *Rosmarinine* (XL): E 235i (−1·86), 213 (−4·73); HCl 237i (−1·06), 213 (−5·0). *Integerrimine* (XLI): E 234 (+3·80), 209 (−4·1); HCl 238 (+2·90), 213 (−4·4). *Usaramine* (XLII): E 231 (+3·36), 206 (−2·0); HCl 238 (+2·48), 213 (−2·1). *Senecionine* (XLIII): E 242 (+2·27), 211 (−7·39); HCl 242 (+1·54), 213 (−9·02); M 248 (+1·02, negative at shorter wavelengths. *Retrorsine* (XLIV): E 239 (+3·11), 211 (−4·65); HCl 242 (+2·35), 214 (−6·52). *Erucifoline* (XLV):

E 244 (+1·18), 211 (−7·2); HCl 246 (+1·24), 224i (−4·52), 215 (−7·5); M 263 (positive), 230 (negative). *Madurensine* (XLVI): E 223 (−1·14), 195 (+5·9); HCl 219 (−4·75). *Senkirkine* (*Renardine*) (XLVII): E 245 (+3·99), 217 (−2·65); HCl 217 (−4·5); M 288 (+2·41), 247 (+1·98), 199 (−13·3). *Jacozine* (XLVIII): E 248 (+0·25), 217 (−6·27); HCl 215 (−7·03). *Seneciphylline* (XLIX): E 244 (+1·59), 214 (−9·3); HCl 243 (+0·84), 212 (−11); M 254 (+0·54), 215 (−9). *Riddelline* (L): E 246 (+0·63), 214 (−6·4); HCl 215 (−5·9). *Spurtioidine* (LI): E 242 (+1·22), 208 (−5·5); HCl 246 (+0·33), 214 (−3·72). *Clivorine* (LII): E 265i (+1·55), 244 (+4·29), 219 (−8·7); HCl 232 (+7·26), 210 (−1·05); M 285 (+3·90), 248 (+3·31), 223 (−11·20).

We thank Prof. Dr F. L. Warren, Cape Town (South Africa), and Dr A. R Mattocks, Carshalton (England), for the samples of some of these alkaloids. G. S. thanks the Deutsche Forschungsgemeinschaft for financial support, which enabled i.a. J. H. and L. H. to work for some time in Bonn.

REFERENCES

1. Birnbaum K. B., Klásek A., Sedmera P., Snatzke G., Johnson L. F., Šantavý F.: Tetrahedron Letters *1971*, 3421.
2. Haas G., Hulbert P. B., Klyne W., Prelog V., Snatzke G.: Helv. Chim. Acta *54*, 491 (1971).
3. Bull L. B., Culvenor C. C. J., Dick A. T.: *The Pyrrolizidine Alkaloids.* North-Holland, Amsterdam 1968.
4. Warren F. L.: Progr. Chem. Org. Nat. Prod. *24*, 329 (1966).
5. Parello J., Picot F.: Tetrahedron Letters *1968*, 5083.
6. Cymerman Craig J., Roy S. K.: Tetrahedron *21*, 401 (1965).
7. Leonard N. J., Locke D. M.: J. Am. Chem. Soc. *77*, 437 (1955).
8. Snatzke G.: Tetrahedron *21*, 413 (1965).
9. Culvenor C. C. J., Heffernan M. L., Woods W. G.: Australian J. Chem. *18*, 1605 (1965).
10. Legrand M., Viennet R.: Compt. Rend. *262*, C, 1290 (1966).
11. Yogev A., Amar D., Mazur Y.: Chem. Commun. *1967*, 339.
12. Scott A. I., Wrixon A. D.: Chem. Commun. *1969*, 1182.
13. Fétizon M., Hanna I.: Chem. Commun. *1970*, 462.
14. Ždanovič E. S., Men'šikov G. P.: Ž. Obšč. Chim. *11*, 835 (1941); Chem. Abstr. *36*, 4123 (1942).
15. Snatzke G., Schwang H., Welzel P. in the book: *Some Newer Physical Methods in Structural Chemistry* (R. Bonnett, J. G. Davis, Eds), p. 199. United Trade Press, London 1967.
16. Snatzke G., Schaffner K.: Helv. Chim. Acta *51*, 986 (1968).
17. Bootsma G. A., Schoone J. C.: Acta Cryst. *22*, 522 (1967).
18. Kanters J. A., Kroon J., Peerdeman A. F., Schoone J. C.: Tetrahedron *23*, 4027 (1967).
19. Karabatsos G. J., Fenoglio D. J.: J. Am. Chem. Soc. *91*, 1124 (1969).
20. Šimánek V., Klásek A., Šantavý F.: This Journal *34*, 1832 (1969).
21. Anand R. D., Hargreaves M. K.: Chem. Commun. *1967*, 421.
22. Barth G., Voelter W., Bunnenberg E., Djerassi C.: Chem. Commun. *1969*, 355.
23. Listowsky I., Englard S., Avigad G.: Biochemistry *8*, 1781 (1969).
24. Listowsky I., Avigad G., Englard S.: J. Org. Chem. *35*, 1080 (1970).
25. Červinka O., Hub L.: This Journal *33*, 2933 (1968).
26. Snatzke G., Ripperger H., Hartmann C., Schreiber K.: Tetrahedron *22*, 3103 (1966).
27. Snatzke G., Eckhardt G.: Tetrahedron *26*, 1143 (1970).
28. Dornhege E., Snatzke G.: Tetrahedron *26*, 3059 (1970).
29. Legrand M., Bucourt R.: Bull. Soc. Chim. France *1967*, 2241.
30. Wolf H.: Tetrahedron Letters *1966*, 5151.

31. Bürer T.: Helv. Chim. Acta *46*, 2388 (1963).
32. Wellman K. M., Laur P. H. A., Briggs W. S., Moscowitz A., Djerassi C.: J. Am. Chem. Soc. *87*, 66 (1965).
33. Mathieson A. McL., Taylor J. C.: Acta Cryst. *16*, 524 (1963).
34. Toniolo C., Perciaccante V., Falcetta J., Rupp R., Goodman M.: J. Org. Chem. *35*, 6 (1970).
35. Bláha K., Frič I.: This Journal *35*, 619 (1970).
36. Klásek A., Sedmera P., Šantavý F.: This Journal *35*, 956 (1970).
37. Klásek A., Sedmera P., Šantavý F.: This Journal *36*, 2205 (1971).
38. Klásek A., Neuner-Jehle N., Šantavý F.: This Journal *34*, 1459 (1969).
39. Robins D. J., Crout D. H. G.: J. Chem. Soc. (C) *1969*, 1386.
40. Robins D. J., Crout D. H. G.: J. Chem. Soc. (C) *1970*, 1334.
41. Červinka O., Hub L.: This Journal *33*, 2927 (1968).
42. Kompiš I., Šantavý F.: This Journal *27*, 1413 (1962).
43. Sedmera P., Klásek A., Šantavý F.: This Journal, in press.
44. Kuhn W.: Ann. Rev. Phys. Chem. *9*, 417 (1958).
45. Culvenor C. C. J., Smith L. W., Willing R. I.: Chem. Commun. *1970*, 65.
46. Fridrichsons J., Mathieson A. McL., Sutor D. J.: Acta Cryst. *16*, 1075 (1963).

Translated by I. Bartošová.

Note added in proof: While this paper was in press, Culvenor C. C. J., Crout D. H. G., Klyne W., Mose W. P., Renwick J. D., Scopes P. M. published a paper on Circular Dichroism of Pyrrolizidine Alkaloids and Related Compounds in J. Chem. Soc. (C) *1971*, 3653.